CERTARA

Understanding Complex Pharmacokinetics

Physiologically-based modeling and simulation explained unusual Pharmacokinetics (PK) and helped an orphan drug achieve approval based on small clinical studies

Background

In rare diseases, with few patients available for clinical study, every data point becomes crucial to understanding a potential therapy's benefit-risk profile. Model-based methods can help by gathering disparate information sources into a cohesive picture of the dose-concentration-effect relationship, enriching the scientific basis for development decisions. By enriching the models with information about physiological changes during maturation or specific disease states, scientists can confidently predict drug exposures and recommend dosing for special populations.

Challenge

A promising new drug formulation for a very rare disease presented a mystery in clinical development. Expected to prove bioequivalent to an approved formulation, the new drug's active metabolite instead seemed to disappear in the blood, with plasma levels well below those needed to show bioequivalence. Yet final metabolites excreted in urine tracked dosing as predicted.

In trials, the drug otherwise proved at least comparable to the approved formulation in safety and efficacy. To move forward, the sponsor needed to understand the drug's unusual dose-concentration relationship, to ensure robust dosing recommendations, and to demonstrate a sound rationale for regulatory approval and labeling.

Solution

Non-compartmental analysis illustrated but could not explain the disparity between dosing and blood concentrations for the new formulation. A team from the sponsor and Certara consultants performed physiologically relevant modeling to describe observed blood levels of key metabolites. The models suggested that extensive first-pass metabolism of the slowly-absorbed drug could explain low plasma concentrations of the active metabolite; the drug had apparently already begun to exert its effect, pre-systemically, on its way into the body.

Challenge

The sponsor sought to understand the unusual PK of an orphan drug in order to develop robust dosing recommendations and gain regulatory approval to treat patients with a rare disease.

Solution

Certara consultants performed physiologically relevant modeling to describe observed blood levels of key metabolites.

Benefit

The model-based analysis successfully quantified the drug's slow absorption and supported dose recommendations for adults as well as children.

To evaluate dosing for pediatric patients, the team evaluated the relationship between dose and exposure across age groups. A model-based on body surface area best described age-related changes in exposure. Using that model, the team simulated metabolite concentrations across a range of dose strategies and age groups, reliably predicting exposures in patients from two years of age through adulthood.

Benefit

The dose simulations were included with the fast-track New Drug Application for the orphan drug. The model-based analysis successfully quantified the drug's slow absorption and supported dose recommendations for adults as well as children.

Impact

The modeling work provided compelling evidence that the sponsor thoroughly understood the compound's dose-concentration behavior and had established safe dosing recommendations. The Food and Drug Administration approved the new drug for use in adult and pediatric patients.

About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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